

REMARKS

Claims 1, 3-4, 8-17 and 28 remain for consideration. Claim 1 has been amended to more particularly claim Applicants' invention. The amendment of claim 1 is supported by the specification, for example, at page 17, lines 5-11 and Examples 2 and 3. No new matter is introduced by the amendment.

Applicants respectfully request reconsideration of the rejections based on the following comments.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1, 3, 4 and 8-17 under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in a way to reasonably convey to a person of skill in the art that the inventors, at the time of filing the application, had possession of the claimed invention. Specifically, the Examiner indicated that the language added in the previous amendment of January 16, 2001 lacked clear support and is, thus, new matter. In the alternative, the Examiner indicated that the language was indefinite, as explained further below with respect to a rejection under §112, second paragraph. Applicants respectfully request reconsideration of the rejection based on the following comments.

Applicants have amended claim 1 to clarify the language noted by the Examiner. As clarified, Applicants believe that the claim is clearly supported by the specification. Applicants respectfully request the withdrawal of the rejection of claims 1, 3, 4 and 8-17 under 35 U.S.C. §112, first paragraph, for lack of written description.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1, 3, 4 and 8-17 under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner pointed to specific language that the Examiner believed was unclear. Applicants have amended claim 1 for clarity. Applicants respectfully request withdrawal of the rejection of claims 1, 3, 4

and 8-17 under 35 U.S.C. §112, second paragraph as being indefinite.

Rejections Under 35 U.S.C. §102(b) Over Cahalan et al.

The Examiner rejected claims 1, 3, 4, 8, 9, 11, 12 and 15 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent 5,308,641 to Cahalan et al. (the Cahalan patent). The Examiner noted that the Cahalan patent disclosed the attachment of a growth factor biomolecule to a substrate. Applicants respectfully request reconsideration based on the following comments.

Applicants' claims indicate that the growth factor associated with the substrate is effective to stimulate association of viable cells with the substrate. Binding of proteins using crosslinking agents is problematic when trying to maintain active growth factors following the crosslinking process. That is the nature of fixation. Crosslinking agents that are effective for fixation, such as dialdehydes, bind indiscriminately to proteins. This indiscriminate bonding is desirable for fixing tissue since it masks antigens found in the tissue that can result in severe immune responses for xenograft tissues. However, this same indiscriminate bonding inactivates enzymes.

Applicants' Examples 2 and 3 demonstrate a successful approach for the crosslinking of VEGF to tissue using a dialdehyde without inactivating the VEGF. As described in Applicants' specification at page 17, line 22 to page 18, line 28, carefully controlled conditions must be used to crosslink the growth factors without inactivation of the growth factors.

The Cahalan patent does not demonstrate the attachment of biomolecules, such as growth factors, while maintaining the effectiveness of the growth factor. Dialdehydes crosslink with proteins in a way that generally results in interference with the protein activity. The Cahalan patent does not provide a reasonable expectation of success with respect to binding growth factors with

dialdehydes while maintaining the activity of the growth factors, as specified in Applicants' claims.

Thus, the Cahalan patent does not anticipate Applicants' claims. Applicants respectfully request withdrawal of the rejection of claims 1, 3, 4, 8, 9, 11, 12 and 15 under 35 U.S.C. §102(b) as being anticipated by the Cahalan patent.

Rejections Over Rodman

The Examiner rejected claims 1, 3, 4, 11, 14, 15 and 28 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent 5,606,026 to Rodman (the Rodman patent). The Examiner cited the Rodman patent for disclosing the TAT protein associated with 2 mm strips. Applicants believe that there was some misunderstanding with respect to the Rodman patent. Applicants respectfully request reconsideration of the rejections over the Rodman patent based on the following comments.

The Rodman patent describes membranes, specifically Immobilon P membranes, that absorb proteins. The proteins are transferred to the membrane from a PAGE electrophoresis gel. Peroxidase labeled antibodies react with the proteins bound to the membrane to label the proteins. **The antibodies do not bind the TAT proteins to the membrane.** Thus, the Rodman patent does not disclose the types of structures disclosed and claimed by Applicants.

Since the Rodman patent does not disclose Applicants' structures, the Rodman patent does not anticipate Applicants' claimed invention. Applicants respectfully request withdrawal of the rejection of claims 1, 3, 4, 11, 14, 15 and 28 under 35 U.S.C. §102(b) as being anticipated by the Rodman patent.

Rejections Over Cahalan et al. and Goldstein

The Examiner rejected claim 10 under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent in view of U.S. Patent 5,613,982 to Goldstein (the Goldstein patent). The Examiner noted that the Cahalan patent disclosed tissue but failed to disclose

particular types of animal tissue. The Examiner cited the Goldstein patent for teaching the use of porcine tissue. Applicants respectfully request reconsideration of the rejection based on the following comments.

As noted above, the Cahalan patent is deficient with respect to disclosing Applicants' claimed invention since the Cahalan patent does not provide a reasonable expectation of achieving active growth factors bound to the substrate. The Goldstein patent describes the inclusion of growth factors in a growth media containing cells, but the Goldstein patent does not describe binding growth factors to substrates. Since the cited references do not disclose the binding of growth factors to a substrate to obtain active growth factors, the combined disclosures of the Cahalan patent and the Goldstein patent do not render Applicants' claimed invention obvious. Applicants respectfully request withdrawal of the rejection of claim 10 under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent in view of the Goldstein patent.

Rejections Over Cahalan et al. and Robertson et al.

The Examiner rejected claim 17 under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent in view of U.S. Patent 3,755,042 to Robertson et al. (the Robertson patent). The Examiner cited the Robertson patent for its disclosure of sterilizing and packaging medical devices. The Examiner indicated that it would be obvious for a person in the art to sterilize and package the Cahalan device for distribution. Applicants respectfully request reconsideration of the rejection based on the following comments.

As noted above, the Cahalan patent is deficient with respect to disclosing Applicants' claimed invention since the Cahalan patent does not provide a reasonable expectation of achieving active growth factors bound to the substrate. The Robertson patent does not teach or suggest growth factors or the bonding of proteins. In addition, the heat sterilization

approaches described in the Robertson patent would be expected to inactivate the growth factors. Thus, the combined disclosures of the Cahalan patent and the Robertson patent do not render Applicants' claimed invention obvious. Applicants respectfully request withdrawal of the rejection of claim 17 under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent in view of the Robertson patent.

Rejection of Claims 13 and 16

The Examiner rejected claims 13 and 16 under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent in view of European application EP 0476983 to Bayne et al. (the Bayne EP application). The Examiner noted that the Cahalan patent did not disclose VEGF growth factors even though other growth factors were described. The Examiner cites the Bayne EP application for disclosing VEGF growth factors used with implants. Applicants respectfully request reconsideration of the rejection based on the following comments.

The Bayne EP application does not teach or suggest the bonding of VEGF to materials to form prostheses. Thus, the Bayne EP application does not make up for deficiencies in the Cahalan patent with respect to crosslinking of growth factors to materials to maintain the activity of the growth factor. Therefore, the cited references do not render the claimed invention obvious. Applicants respectfully request withdrawal of the rejection of claims 13 and 16 under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent in view of European application the Bayne EP application.

CONCLUSIONS

In view of the foregoing amendments and remarks, Applicants submit that the application is in condition for allowance, and such action is respectfully requested. The Examiner is invited to telephone the undersigned attorney to discuss any questions or comments that the Examiner may have.

The Director of the Patent and Trademark Office is authorized to charge any fee deficiency required by this paper or credit any overpayment to Deposit Account No. 23-1123.

Respectfully submitted,

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PSD:

MARKED-UP CLAIM AMENDMENTS

Claim 1 is edited as follows:

1. (Four Times Amended) A prosthesis comprising a substrate and a polypeptide growth factor associated with the substrate by covalent bonding using crosslinking agents, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations, wherein the crosslinking agents comprise at least two aldehyde functional groups [that are transformed into other functional groups linking] that form covalent bonds to link the crosslinking agent with the polypeptide growth factor and the substrate, the polypeptide growth factor associated with the substrate being effective to stimulate association of viable cells with the substrate.